SEQUENCE LISTING

<110> Stoddard, Barry L.
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<120> Crystal of a Truncated Protein Construct Containing a
      Coagulation Factor VIII C2 Domain in the Presence or
      Absence of a Bound Ligand and Methods of Use Thereof

<130> 14538A-005310US

<140> US 10/049,399
<141> Not yet assigned

<150> US 60/148,907
<151> 1999-08-13

<150> WO PCT/US00/22226
<151> 2000-08-11

<160> 12

<170> PatentIn Ver. 2.1

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<213> Homo sapiens

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Arg Pro Pro Trp Met Gly Leu Leu Gly Pro Thr Ile Gln Ala Glu Val
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Tyr Asp Thr Val Val Ile Thr Leu Lys Asn Met Ala Ser His Pro Val
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Leu Val Cys Arg Glu Gly Ser Leu Ala Lys Glu Lys Thr Gln Thr Leu
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His Lys Phe Ile Leu Leu Phe Ala Val Phe Asp Glu Gly Lys Ser Trp
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His Ser Glu Thr Lys Asn Ser Leu Met Gln Asp Arg Asp Ala Ala Ser
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Ala Arg Ala Trp Pro Lys Met His Thr Val Asn Gly Tyr Val Asn Arg
225             230             235                 240
Ser Leu Pro Gly Leu Ile Gly Cys His Arg Lys Ser Val Tyr Trp His
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Val Ile Gly Met Gly Thr Thr Pro Glu Val His Ser Ile Phe Leu Glu
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Gly His Thr Phe Leu Val Arg Asn His Arg Gln Ala Ser Leu Glu Ile
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Ser Pro Ile Thr Phe Leu Thr Ala Gln Thr Leu Leu Met Asp Leu Gly
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Gln Phe Leu Leu Phe Cys His Ile Ser Ser His Gln His Asp Gly Met
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Glu Ala Tyr Val Lys Val Asp Ser Cys Pro Glu Glu Pro Gln Leu Arg
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Met Lys Asn Asn Glu Glu Ala Glu Asp Tyr Asp Asp Asp Leu Thr Asp
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Ser Glu Met Asp Val Val Arg Phe Asp Asp Asp Asn Ser Pro Ser Phe
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Ile Gln Ile Arg Ser Val Ala Lys Lys His Pro Lys Thr Trp Val His
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Tyr Ile Ala Ala Glu Glu Glu Asp Trp Asp Tyr Ala Pro Leu Val Leu
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2

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Thr Phe Lys His Lys Met Val Tyr Glu Asp Thr Leu Thr Leu Phe Pro
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Phe Ser Gly Glu Thr Val Phe Met Ser Met Glu Asn Pro Gly Leu Trp
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Asp Ser Tyr Glu Asp Ile Ser Ala Tyr Leu Leu Ser Lys Asn Asn Ala
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His Gly Leu Ser Leu Ser Asp Leu Gln Glu Ala Lys Tyr Glu Thr Phe
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Ser Asp Asp Pro Ser Pro Gly Ala Ile Asp Ser Asn Asn Ser Leu Ser
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Glu Met Thr His Phe Arg Pro Gln Leu His His Ser Gly Asp Met Val
        835             840             845

Phe Thr Pro Glu Ser Gly Leu Gln Leu Arg Leu Asn Glu Lys Leu Gly
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            885             890             895

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            900             905             910

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Ser Lys Leu Leu Glu Ser Gly Leu Met Asn Ser Gln Glu Ser Ser Trp
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Gly Lys Asn Val Ser Ser Thr Glu Ser Gly Arg Leu Phe Lys Gly Lys
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Arg Ala His Gly Pro Ala Leu Leu Thr Lys Asp Asn Ala Leu Phe Lys
        980             985             990

Val Ser Ile Ser Leu Leu Lys Thr Asn Lys Thr Ser Asn Asn Ser Ala
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    1010            1015            1020

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Lys Val Thr Pro Leu Ile His Asp Arg Met Leu Met Asp Lys Asn Ala
            1045            1050            1055

Thr Ala Leu Arg Leu Asn His Met Ser Asn Lys Thr Thr Ser Ser Lys
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Ser Val Glu Gly Gln Asn Phe Leu Ser Glu Lys Asn Lys Val Val Val
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Gly Lys Gly Glu Phe Thr Lys Asp Val Gly Leu Lys Glu Met Val Phe
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Lys Glu Thr Leu Ile Gln Glu Asn Val Val Leu Pro Gln Ile His Thr
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Val Thr Gly Thr Lys Asn Phe Met Lys Asn Leu Phe Leu Leu Ser Thr
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Thr Ala His Phe Ser Lys Lys Gly Glu Glu Glu Asn Leu Glu Gly Leu
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Glu Lys Gly Ala Ile Thr Gln Ser Pro Leu Ser Asp Cys Leu Thr Arg
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Ser His Ser Ile Pro Gln Ala Asn Arg Ser Pro Leu Pro Ile Ala Lys
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Arg Glu Val Gly Ser Leu Gly Thr Ser Ala Thr Asn Ser Val Thr Tyr
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Ser Gly Lys Val Glu Leu Leu Pro Lys Val His Ile Tyr Gln Lys Asp
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Glu Ala Asn Arg Pro Gly Lys Val Pro Phe Leu Arg Val Ala Thr Glu
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Ser Ser Ala Lys Thr Pro Ser Lys Leu Leu Asp Pro Leu Ala Trp Asp
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Asn His Tyr Gly Thr Gln Ile Pro Lys Glu Glu Trp Lys Ser Gln Glu
   1570              1575              1580

Lys Ser Pro Glu Lys Thr Ala Phe Lys Lys Lys Asp Thr Ile Leu Ser
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Asp Asp Thr Ile Ser Val Glu Met Lys Lys Glu Asp Phe Asp Ile Tyr
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His Tyr Phe Ile Ala Ala Val Glu Arg Leu Trp Asp Tyr Gly Met Ser
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Asn Gln Ala Ser Arg Pro Tyr Ser Phe Tyr Ser Ser Leu Ile Ser Tyr
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Glu Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys
            1795            1800            1805

Pro Asn Glu Thr Lys Thr Tyr Phe Trp Lys Val Gln His His Met Ala
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Pro Thr Lys Asp Glu Phe Asp Cys Lys Ala Trp Ala Tyr Phe Ser Asp
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Val Cys His Thr Asn Thr Leu Asn Pro Ala His Gly Arg Gln Val Thr
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Val Gln Glu Phe Ala Leu Phe Phe Thr Ile Phe Asp Glu Thr Lys Ser
            1875            1880            1885

Trp Tyr Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala Pro Cys Asn
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Ile Gln Met Glu Asp Pro Thr Phe Lys Glu Asn Tyr Arg Phe His Ala
1905            1910            1915            1920

Ile Asn Gly Tyr Ile Met Asp Thr Leu Pro Gly Leu Val Met Ala Gln
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Asp Gln Arg Ile Arg Trp Tyr Leu Leu Ser Met Gly Ser Asn Glu Asn
            1940            1945            1950

Ile His Ser Ile His Phe Ser Gly His Val Phe Thr Val Arg Lys Lys
    1955            1960            1965

Glu Glu Tyr Lys Met Ala Leu Tyr Asn Leu Tyr Pro Gly Val Phe Glu
    1970            1975            1980

Thr Val Glu Met Leu Pro Ser Lys Ala Gly Ile Trp Arg Val Glu Cys
1985            1990            1995            2000

Leu Ile Gly Glu His Leu His Ala Gly Met Ser Thr Leu Phe Leu Val
            2005            2010            2015

Tyr Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile
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Lys Leu Ala Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr
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Lys Glu Pro Phe Ser Trp Ile Lys Val Asp Leu Leu Ala Pro Met Ile
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Tyr Ile Ser Gln Phe Ile Ile Met Tyr Ser Leu Asp Gly Lys Lys Trp
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Gln Thr Tyr Arg Gly Asn Ser Thr Gly Thr Leu Met Val Phe Phe Gly
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Asn Val Asp Ser Ser Gly Ile Lys His Asn Ile Phe Asn Pro Pro Ile
   2130                2135                2140

Ile Ala Arg Tyr Ile Arg Leu His Pro Thr His Tyr Ser Ile Arg Ser
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Thr Leu Arg Met Glu Leu Met Gly Cys Asp Leu Asn Ser Cys Ser Met
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Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala Gln Ile Thr Ala
             2180                2185                2190

Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser Pro Ser Lys Ala
          2195                2200                2205

Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg Pro Gln Val Asn
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Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Gln Lys Thr Met Lys Val
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Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly His Gln Trp Thr
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Leu Phe Phe Gln Asn Gly Lys Val Lys Val Phe Gln Gly Asn Gln Asp
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Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Pro Leu Leu Thr Arg
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Tyr Leu Arg Ile His Pro Gln Ser Trp Val His Gln Ile Ala Leu Arg
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11

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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:human Factor
      VIII C2 domain

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      mutation)

<220>
<221> VARIANT
<222> (35)
<223> Xaa = Lys (wild-type) or Gln, Leu or Gly
      (hemophilia A mutations)

<220>
<221> VARIANT
<222> (54)
<223> Xaa = Pro (wild-type) or Cys (hemophilia A
      mutation)

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<223> Xaa = Met (wild-type) or Val (hemophilia A
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<220>
<221> VARIANT
<222> (73)
<223> Xaa = Thr (wild-type) or Ala (hemophilia A
      mutation)

<220>
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<222> (132)
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Gln Ile Thr Xaa Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser
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Pro Ser Xaa Ala Arg Leu His Leu Gln Gly Arg Ser Asn Ala Trp Arg
        35   40   45

Pro Gln Val Asn Asn Xaa Lys Glu Trp Leu Gln Val Asp Phe Gln Lys
        50   55   60

Thr Xaa Lys Val Thr Gly Val Thr Xaa Xaa Gly Val Lys Ser Leu Leu
65   70   75   80

Thr Ser Met Tyr Val Lys Glu Phe Leu Xaa Ser Ser Ser Gln Asp Gly
                85   90   95

His Gln Trp Thr Leu Phe Phe Gln Asn Gly Lys Val Lys Val Xaa Gln
            100   105   110

Gly Asn Gln Asp Ser Phe Thr Pro Val Val Asn Ser Leu Asp Pro Xaa
        115   120   125

Leu Leu Thr Xaa Tyr Leu Xaa Ile His Pro Gln Ser Trp Val His Gln
    130   135   140

Ile Ala Leu Xaa Met Glu Val Leu Xaa Cys Glu Ala Gln Asp Leu Tyr
145   150   155   160

<210> 8
<211> 160
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:murine Factor
      VIII C2 domain

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Ser Cys Ser Ile Pro Leu Gly Met Glu Ser Lys Val Ile Ser Asp Thr
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Gln Ile Thr Ala Ser Ser Tyr Phe Thr Asn Met Phe Ala Thr Trp Ser
            20   25   30

Pro Ser Gln Ala Arg Leu His Leu Gln Gly Arg Thr Asn Ala Trp Arg
        35   40   45

Pro Gln Val Asn Asp Pro Lys Gln Trp Leu Gln Val Asp Leu Gln Lys
        50   55   60

Thr Met Lys Val Thr Gly Ile Ile Thr Gln Gly Val Lys Ser Leu Phe
65   70   75   80

Thr Ser Met Phe Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
                85   90   95

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His His Trp Thr Gln Ile Leu Tyr Asn Gly Lys Val Lys Val Phe Gln
            100             105             110

Gly Asn Gln Asp Ser Ser Thr Pro Met Met Asn Ser Leu Asp Pro Pro
            115             120             125

Leu Leu Thr Arg Tyr Leu Arg Ile His Pro Gln Ile Trp Glu His Gln
        130             135             140

Ile Ala Leu Arg Leu Glu Ile Leu Gly Cys Glu Ala Gln Gln Gln Tyr
145             150             155             160


<210> 9
<211> 160
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:canine Factor
      VIII C2 domain

<400> 9
Ser Cys Ser Met Pro Leu Gly Met Glu Ser Lys Ala Ile Ser Asp Ala
  1           5               10              15

Gln Ile Thr Ala Ser Ser Tyr Leu Ser Ser Met Leu Ala Thr Trp Ser
            20              25              30

Pro Ser Gln Ala Arg Leu His Leu Gln Gly Arg Thr Asn Ala Trp Arg
            35              40              45

Pro Gln Ala Asn Asn Pro Lys Glu Trp Leu Gln Val Asp Phe Arg Lys
        50              55              60

Thr Met Lys Val Thr Gly Ile Thr Thr Gln Gly Val Lys Ser Leu Leu
65              70              75              80

Ile Ser Met Tyr Val Lys Glu Phe Leu Ile Ser Ser Ser Gln Asp Gly
                85              90              95

His Asn Trp Thr Leu Phe Leu Gln Asn Gly Lys Val Lys Val Phe Gln
            100             105             110

Gly Asn Arg Asp Ser Ser Thr Pro Val Arg Asn Arg Leu Glu Pro Pro
            115             120             125

Leu Val Ala Arg Tyr Val Arg Leu His Pro Gln Ser Trp Ala His His
        130             135             140

Ile Ala Leu Arg Leu Glu Val Leu Gly Cys Asp Thr Gln Gln Pro Ala
145             150             155             160


<210> 10
<211> 160
<212> PRT
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<220>
<223> Description of Artificial Sequence:porcine Factor
       VIII C2 domain

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Ser Cys Ser Met Pro Leu Gly Met Gln Asn Lys Ala Ile Ser Asp Ser
  1   5   10   15

Gln Ile Thr Ala Ser Ser His Leu Ser Asn Ile Phe Ala Thr Trp Ser
            20   25   30

Pro Ser Gln Ala Arg Leu His Leu Gln Gly Arg Thr Asn Ala Trp Arg
        35   40   45

Pro Arg Val Ser Ser Ala Glu Glu Trp Leu Gln Val Asp Leu Gln Lys
        50   55   60

Thr Val Lys Val Thr Gly Ile Thr Thr Gln Gly Val Lys Ser Leu Leu
 65   70   75   80

Ser Ser Met Tyr Val Lys Glu Phe Leu Val Ser Ser Ser Gln Asp Gly
                85   90   95

Arg Arg Trp Thr Leu Phe Leu Gln Asp Gly His Thr Lys Val Phe Gln
            100   105   110

Gly Asn Gln Asp Ser Ser Thr Pro Val Val Asn Ala Leu Asp Pro Pro
            115   120   125

Leu Phe Thr Arg Tyr Leu Arg Ile His Pro Thr Ser Trp Ala Gln His
    130   135   140

Ile Ala Leu Arg Leu Glu Val Leu Gly Cys Glu Ala Gln Asp Leu Tyr
145   150   155   160

<210> 11
<211> 159
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:porcine Factor
       V C2 domain

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Gly Cys Ser Thr Pro Leu Gly Met Glu Asn Gly Lys Ile Glu Asn Lys
  1   · 5   10   15

Gln Ile Thr Ala Ser Ser Phe Lys Lys Ser Trp Trp Gly Asp Tyr Trp
            20   25   30

Glu Pro Phe Arg Ala Arg Leu Asn Ala Gln Gly Arg Val Asn Ala Trp
        35   40   45

Gln Ala Lys Ala Asn Asn Asn Lys Gln Trp Leu Glu Ile Asp Leu Leu
        50   55   60

Lys Ile Lys Lys Ile Thr Ala Ile Ile Thr Gln Gly Cys Lys Ser Leu
 65   70   75   80

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Ser Ser Glu Met Tyr Val Lys Ser Tyr Thr Ile His Tyr Ser Glu Gln
                85   90   95

Gly Val Glu Trp Lys Pro Tyr Arg Leu Lys Ser Ser Met Val Asp Lys
            100   105   110

Ile Phe Glu Gly Asn Thr Asn Thr Lys Gly His Val Lys Asn Phe Phe
        115   120   125

Asn Pro Pro Ile Ile Ser Arg Phe Ile Arg Val Ile Pro Lys Thr Trp
    130   135   140

Asn Gln Ser Ile Ala Leu Arg Leu Glu Leu Phe Gly Cys Asp Ile
145   150   155

<210> 12
<211> 150
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:human Factor
      VIII C1 domain

<400> 12
Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His Ile Arg Asp Phe
  1   5   10   15

Gln Ile Thr Ala Ser Gly Gln Tyr Gly Gln Trp Ala Pro Lys Leu Ala
            20   25   30

Arg Leu His Tyr Ser Gly Ser Ile Asn Ala Trp Ser Thr Lys Glu Trp
            35   40   45

Ile Lys Val Asp Leu Leu Ala Pro Met Ile Ile His Gly Ile Lys Thr
        50   55   60

Gln Gly Ala Arg Gln Lys Phe Ser Ser Leu Tyr Ile Ser Gln Phe Ile
 65   70   75   80

Ile Met Tyr Ser Leu Asp Gly His His Trp Gln Thr Tyr Arg Gly Asn
                85   90   95

Ser Thr Gly Thr Leu Met Val Phe Gln Gly Asn Val Asp Ser Ser Gly
            100   105   110

Ile Lys His Asn Ile Phe Asn Pro Pro Ile Ile Ala Arg Tyr Ile Arg
        115   120   125

Leu His Pro Thr His Tyr Ser Ile Arg Ser Thr Leu Arg Met Glu Leu
    130   135   140

Met Gly Cys Asp Leu Asn
145   150